Steroid Hormones--8 Nov. 2002

1) How many carbon atoms do aldosterone, cortisol, testosterone, and estradiol contain? Draw their structures.

Aldosterone = 21
Cortisol = 21
Testosterone = 19
Estradiol = 18

[Look up the structures]

2) Describe the consequences of CYP21 and CYP11B1 deficiencies.

Loss of either CYP21 or CYP11B1 causes congenital adrenal hyperplasia (CAH), masculinization of the female genitalia and premature virilization in male infants. CYP11B1 differs from CYP21 in that it is also associated with hypertension resulting from the accumulation of 11-deoxycorticosterone, a mineralocorticoid.

There are two types of CYP21 deficiency that we discussed: the simple virilizing form and the salt losing form. The difference is that in the simple form, the enzyme is only partially defective and circulating amounts of cortisol and aldosterone can be corrected by adreanl hyperplasia. In the salt losing form the enzyme is completely deficient and adreanl hyperplasia cannot correct the levels of these circulating hormones. When the child is born they won't have a stress response or the ability to properly regulate their electrolytes and will need immediate attention to correct the electrolyte imbalance. This child will need both mineralocorticoids and gluccocorticoids to survive. In the simple form, the levels of aldosterone and cortisol will be corrected by CAH and will be present at normal amounts in the blood. In the slat losing form, the amounts of aldosterone and cortisol should be VERY low or absent.

Why do you get adrenal hyperplasia in either deficiency? Because both lower or prevent the production of cortisol (and aldosterone) and the low levels of cortisol (and aldosterone) are sensed by the hypothalamus. this stimulates the hypothalmus to release corticotropin-releasing hormone (CRH). CRH goes to the pituitary gland and this stimlates the release of adrenocorticotropic hormone (ACTH). Increased ACTH then stimulates growth of the adrenal cortex and increases the synthesis of the enzymes in the cortisol/aldosterone biosynthetic pathways.

In either case, without CYP21 or CYP11B1, you end up making more androstenedione (a weak androgen) instead of more cortisol (or aldosterone). The increased levels of androstendione causes the masculinization of the female genitalia and premature virilization in male infants.

A deficiency in CYP11B2 was not really discussed in lecture but it also causes masulinization of female genitalia and decreased synthesis of aldosterone. Synthesis of cortisol is unaffected. Electrolyte imbalance and hypertension similar to that observed to CYP11B1 may occur if the CAH casues enough 11-deoxycorticosterone to accumulate. The CAH in this case is caused by a disruption of the renin-angiotension-aldosterone system that senses and corrects mineralocorticoid levles like the cortisol-CRH-ACTH system does.

3) Describe the general mechanism of action of steroid hormones.

In general, steroid hormones bind to their receptors in target cells. The receptors, in the absence of ligand (ligand means steroid horomone in this case), are found in an inactive complex with heat shock proteins (HSPs). Once the hormone binds to its receptor the HSPs dissociate and the ligand-bound receptor can interact with steroid hormone response elements (HREs) of the target genes regulated by the hormone in the nucleus. Binding of the ligand-bound receptor to the HRE promotes association of coactivator proteins. Together, the ligand-bound receptor and the coactivators recruit transcription factors that then increase the transcription of the hormone-responsive gene.

Additional note: In fact, its more complicated than this because some genes transcription is turned OFF in response to steroids. But the above simple mechanism is sufficient for a basic understanding of how steroids elicit responses in their target cells. They elicit responses by changing the levels of transcription of hormone responsive genes.

4) Describe the basis for Apparent Mineralocorticoid Excess (AME) syndrome.

AME results from the loss of renal 11-□□hydroxysteroid dehydrogenase (11 □□HSD). 11 □□HSD interconverts cortisol (active glucocorticoid) to cortisone (inactive glucocorticoid). How can loss of something involved in interconverting glucocorticoids present in a patient like an excess of mineralocorticoids?

Well, it turns out that receptors to mineralocorticoids also have high affinity for glucocorticoids and in general there are much higher levels of glucocorticoids in circulation than mineralocorticoids. In order to get a selective mineralocorticoid response in cells (such as in the tubule of the kidney where mineralocorticoids are important regulators of salt retention), the cells that are the targets of mineralocorticoids contain high levels of 11 □□HSD. This converts the cortisol into its inactive form and thus only the remaining, unaltered aldosterone will bind to its receptor and excert its effects in the target cell. But, if you lack 11 □□HSD, then cortisol will get into the kidney cells, not be inactivated, and act just like aldosterone and cause the same physiological responses as excess aldosterone (i.e. apparent mineralocorticoid excess). This results in hypertension and excess loss of potassium (hypokalemia). Aldosterone's normal function is to help you reabsorb NaCl and water from the kidney tubule (prevent its loss in the urine) and to promote excretion into the kidney tubule of potassium and protons.

5) List the modifications to androgens and estrogens that make them more potent.

Both estrogens and testosterones are made more potent by the addition of the 17-OH group. In addition, modifications that make the rings more planar increase their potency. For estrogens, the aromatization of the the A ring that occurs during the formation of estrone makes the ring structure more planar. For testosterones, the reduction of the 4-5 carbon-carbon double bond yields dihydrotestostereone and this makes the ring structure more planar.

6) What genetics defect causes feminization of male genitalia and why?

Loss of 5-alpha-reductase 2 activity causes feminization of the male genitalia. This happens because the individual cannot make the most potent testosterone, dihydrotestosterone. About 10% of circulating testosterone (of all forms) is the dihydro form. This form is necessary to develop secondary sexual characteristics in males. Individuals with 5-alpha-reductase 2 deficiency oftentimes have the external appearance of a hermaphrodite with a small penis and a blind ending vagina.

Loss of a functional androgen receptor. Complete loss of the androgen receptor results in a XY males that act and look externally exactly like normal XX females. This is called complete testicular feminization. These individuals could go their whole lives not realizing that they are genetically an XY male. This is sometimes discovered when they try and have children because they to not have a complete female reproductive tract and are sterile.